

(12) UK Patent Application (19) GB (11) 2 306 885 (13) A

(43) Date of A Publication 14.05.1997

(21) Application No 9522885.4	(51) INT CL ⁶ A61K 9/06
(22) Date of Filing 08.11.1995	
(71) Applicant(s) Reckitt & Colman Products Limited (Incorporated in the United Kingdom) One Burlington Lane, LONDON, W4 2RW, United Kingdom	(52) UK CL (Edition O) A5B BLD B33Y B330 B42Y B420 B421 B46Y B462 B48Y B482 B483 B50Y B503 B53Y B531 B55Y B552 B57Y B575 B576 B58Y B586 B64Y B642 B644 B823 B826
(72) Inventor(s) Stephen Poile	(56) Documents Cited EP 0272045 A2 EP 0271332 A2 WO 93/20799 A1
(74) Agent and/or Address for Service Simon Eddowes Reckitt & Colman Plc, Group Patents Department, Dansom Lane, HULL, HU8 7DS, United Kingdom	(58) Field of Search UK CL (Edition O) A5B BLB BLC BLD BNB INT CL ⁶ A61K 9/06 9/08 9/10 9/10 ONLINE: WPI, CLAIMS

(54) Supersaturated pharmaceutical compositions

(57) A pharmaceutical composition for topical application comprising
a) a pharmaceutically active agent, and
b) a pharmaceutically acceptable vehicle,
the composition having a pH of 7 to 12 or a pH of 3 to 4,
characterised in that the pharmaceutically active agent is dissolved at or below its saturation concentration
and that the composition becomes supersaturated when the pH is changed to between 4.5 to 6.5.

GB 2 306 885 A

Figure 1

Ketoprofen Solubility at different pH values

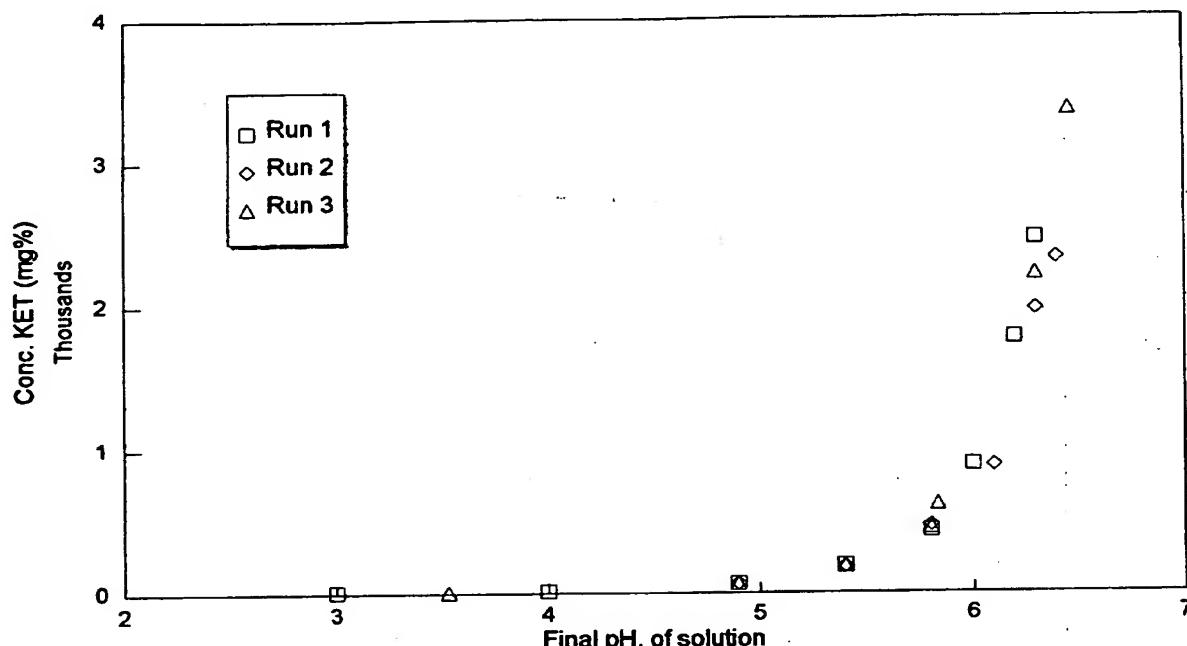


Figure 2

Ketoprofen Theoretical Limits of Supersaturation From a saturated solution at pH 6.4

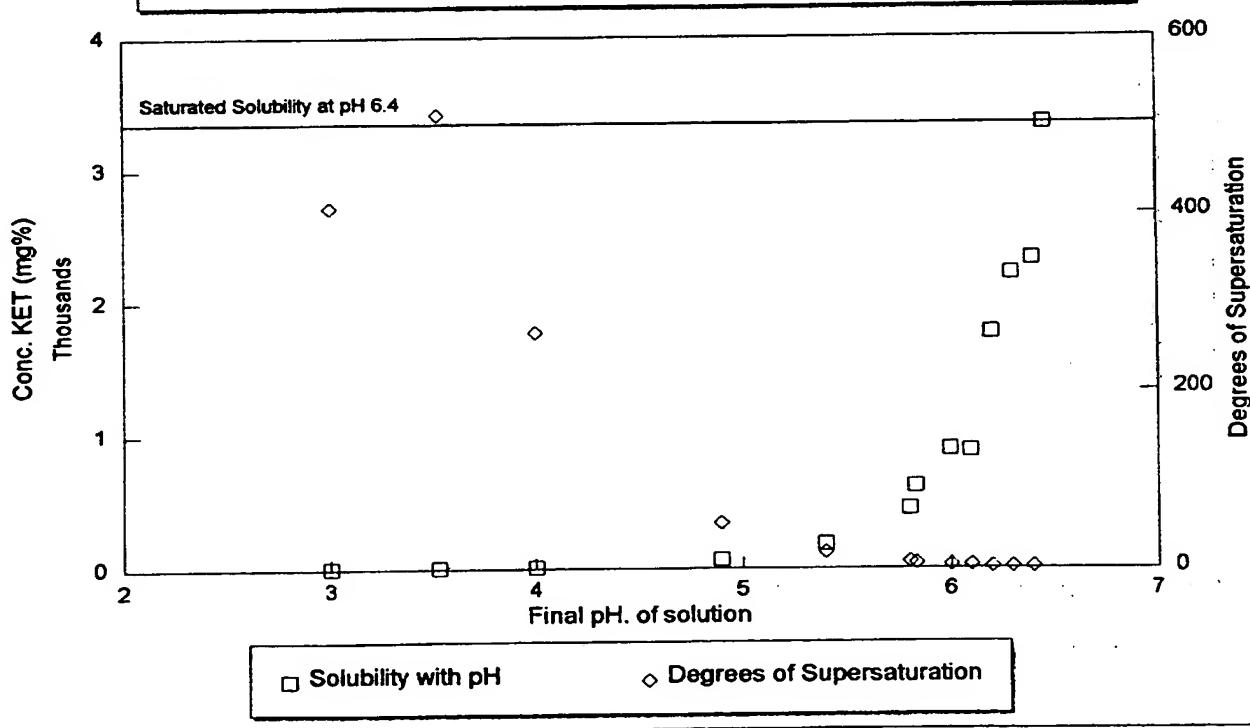


Figure 3

4x Supersaturated solution of Ketoprofen
Produced by pH change

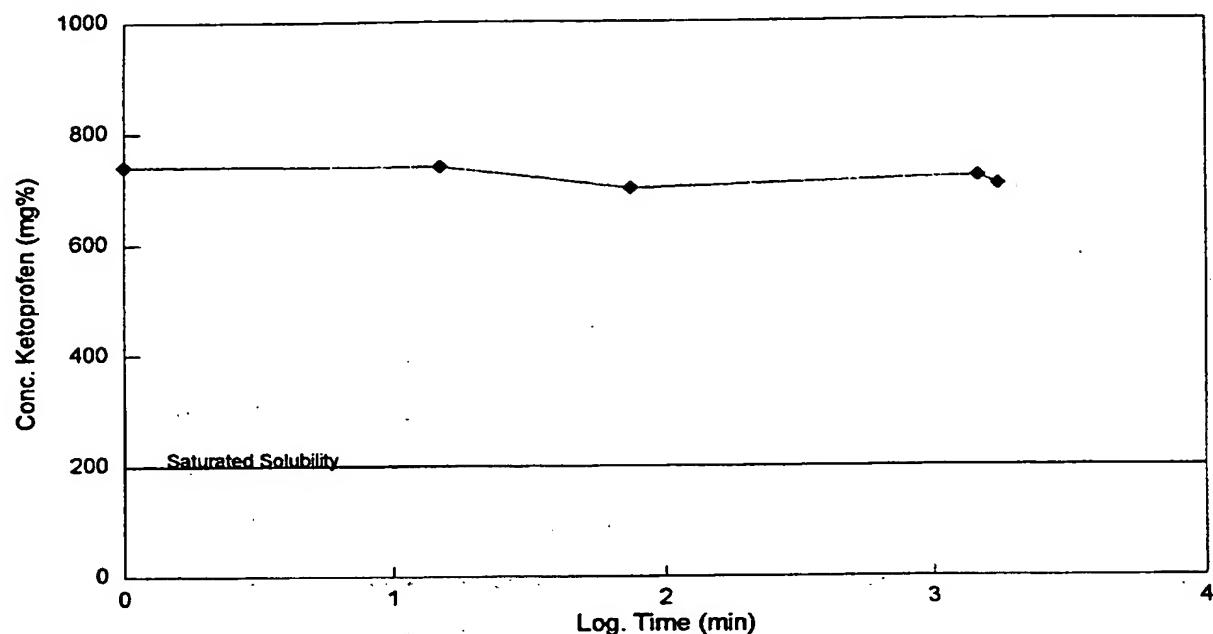
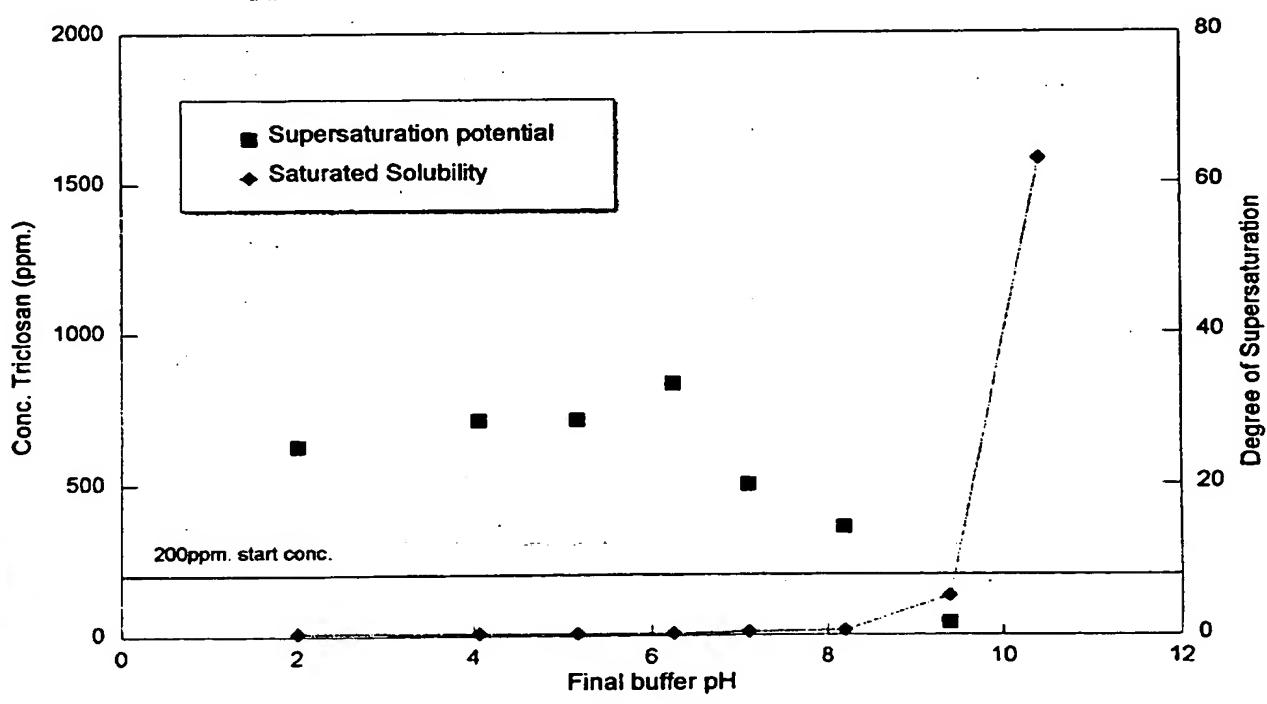


Figure 4

Potential for Triclosan Supersaturation



Improvements in or relating to Organic Compositions

The present invention relates to a pharmaceutical composition and in particular to a composition for 5 topical application to the human or animal body.

It has long been known that in order to effectively deliver therapeutic levels of active material topically, either for local or systemic effect, there is a need to 10 optimise the delivery system to maximise percutaneous penetration.

A number of solutions have been proposed with varying degrees of success. These include use of 15 penetration enhancers, iontophoresis, phonophoresis and supersaturation. Whilst supersaturated solutions have been clearly demonstrated as being effective in promoting percutaneous penetration they are difficult to use because they are not very stable. Thus solutions of the 20 active agents may only be made supersaturated a short time before application to the skin, which is difficult if they are to be used by general consumers.

One solution has been to create a supersaturated 25 solution of the active agent from a subsaturated solution of the drug in a mixture of a volatile and a non-volatile solvent . The mechanism behind this approach is that

when applied topically, the volatile solvent rapidly evaporates causing the drug concentrate remaining in the non-volatile solvent to increase to a supersaturated level. This increase in drug concentration to 5 supersaturation has been found to increase the rate of drug penetration into the skin.

However, a disadvantage of this system is that the volatile (eg ethanol) causes damage to the skin lipid 10 membrane and may also be taken up by the body. Also, packaging has to be sophisticated enough to prevent evaporation of the volatile - which leads to long term storage difficulties.

15 Another method to produce supersaturated compositions for the percutaneous penetration of active agents has been to produce a composition for topical application made up of two liquid phases, one containing the drug which has been dissolved in that phase and the 20 other, which may be physically and/or chemically different from the first (but miscible with it), optionally also containing the same drug dissolved therein. The concentration of drug in each phase is such that, on admixture of the phases, the resultant 25 total drug concentration is greater than the saturated drug solubility in the initially formed mixture of

phases , thereby producing a mixture supersaturated with the drug.

This enables improved drug penetration to be obtained by creating a supersaturated drug solution using 5 a two phase composition mixed *in situ* without the need for the evaporation of a volatile. However, such a two-phase composition requires sophisticated packaging technology to ensure that the two phases are kept apart prior to application, and subsequently there is a need 10 for accurate dose administration of each phase upon application, concomitant with a thorough mixing during application. This approach therefore has limited application due to the cost and sophistication of packaging technology.

15

We have now found that supersaturated compositions may be produced *in situ* on the skin without the drawbacks associated with the above described volatile solvent or two-phase compositions. It is known that many 20 pharmaceutically active substances have very different solubilities in particular liquids depending upon the pH conditions. Thus if such an active is dissolved in a particular solvent at one pH and the pH is changed the resultant decrease in solubility may be sufficient to 25 produce a supersaturated solution. We have now found that by bringing an appropriate solution of this type into contact with the skin, the skin's innate ability to

buffer applied liquids to a pH of 4.5 to 6.5 may be sufficient to cause such a solubility change, and therefore produce a supersaturated solution.

5 . . . There is therefore provided a pharmaceutical composition for topical application comprising
a) a pharmaceutically active agent, and
b) a pharmaceutically acceptable vehicle, the composition having a pH of 7 to 12 or a pH of 3 to 4,
10 . . . characterised in that the pharmaceutically active agent is dissolved at or below its saturation concentration and that the composition becomes supersaturated when the pH is changed to between 4.5 to 6.5.

15 . . . Compositions of the above type are suitable to provide active agents to act locally (ie at the site of application) or systemically (ie transdermal application).

20 . . . Further according to the invention there is provided a method for topical application of an active agent comprising applying to an area of the surface of a body a composition comprising a pharmacologically effective amount of a pharmaceutically active agent dissolved in a pharmaceutically acceptable vehicle, the composition having a pH of 7 to 12 or a pH of 3 to 4 before

application to the said surface of the body,
characterised in that the pharmaceutically active agent
is dissolved at or below its saturation concentration
before application to the said surface of the body but
5 becomes supersaturated following the pH change to 4.5 to
6.5 consequent upon the application to the said surface
of the body.

Preferably the compositions of the invention contain
10 an anti-nucleating agent, enabling substantial reduction
in drug precipitation when the composition becomes
supersaturated. In addition, the incorporation of an
anti-nucleating agent, by stabilising the supersaturated
state, enables still higher degrees of supersaturation
15 of the active agent.

Preferably, when present the anti-nucleating agent
is used in an amount of up to 20%, more preferably from
0.01 to 5.0%, most preferably from 0.1 to 2.0% by weight,
20 based on the total weight of the composition.

The anti-nucleating agent should be soluble in the
composition. Examples of suitable anti-nucleating agents
are hydroxy alkylcelluloses, such as
25 hydroxypropylmethylcellulose and hydroxypropylcellulose,
polyvinyl pyrrolidone and polyacrylic acid. A mixture of
two or more different anti-nucleating agents may be used.

The choice of suitable anti-nucleating agent will depend upon the particular active agent and the particular vehicle being used, but suitable anti-nucleating agents can readily be chosen by simple experiment. This may be done, for example, by preparing samples of the desired final supersaturated active agent solution containing a selection of anti-nucleating agents (in say 1% concentration), one to each sample; allowing the samples to stand for, say two hours and noting which solutions have remained clear, and thus stable. Further standard techniques may be used to quantify the effect observed.

A very wide range of active agents and vehicles may be used in the compositions of the invention the only criteria, other than pharmaceutical acceptability, being that the active agent is soluble in the vehicle at a pH within the range of 7 to 12 or 3 to 4 and substantially less soluble in the vehicle at any pH within the range of 4.5 to 6.5.

The degree of improvement in active agent penetration will depend largely upon the ratio of the supersaturated concentration (ie the actual concentration of the active agent in the composition after the pH change on the skin) to the saturation concentration (the

theoretical concentration at which the vehicle would be saturated with the active agent at the particular pH of the composition on the skin).

5 Improvements in penetration may be produced at any ratios greater than 1:1. For slow penetration ratios of from 2:1 to 10:1 may be useful and for rapid penetration ratios of greater than 10:1 may be useful.

10 The compositions of the present invention may produce extremely high ratios of supersaturation of from 2:1 to 500:1, preferably from 2:1 to 50:1.

It will be clear to those skilled in the art that
15 the selection of active agent, active agent concentration and vehicle will be inter-related, each depending to some extent upon the properties of the other. Normally a suitable active agent will be selected and the concentration thereof, plus the specific vehicle or
20 mixtures thereof, will be chosen such that the active agent will exhibit the solubility and supersaturation properties required in the compositions of the invention. Such combinations may easily be selected by simple experimentation or by the use of published values for
25 solubility etc.

Suitable vehicles for use in the compositions of the invention will be those in which the active agents will be ionisable. More preferably the vehicles will be at least partly aqueous and most preferably they will be 5 predominantly water.

It will be understood that the vehicles used in the compositions of the invention may be mixtures of two or more components as long as all of these components are 10 miscible. Whilst it is most preferred that the vehicles of the compositions of the invention are water they may also be for example mixtures of water and alcohols (eg ethanol or propylene glycol).

15 Preferred active agents for use in the compositions of the invention are those which are ionised in the pH range of the compositions (ie 3 to 4 or 7 to 12). Furthermore, it is also preferred that the active agents will be substantially unionised at the pH range of the 20 compositions after application to the surface of a body (ie from 4.5 to 6.5).

More preferably the active agents used in the compositions of the invention will be acids with a pKa of 25 6.5 to 10, bases with a pKa of 4 to 4.5, or amphoteric agents with an acid pKa of 6.5 to 10 and a base pKa of 4 to 4.5.

Most preferably the active agents used in the compositions of the invention will be substantially ionised at some point between the pH range 7.5 to 10 and 5 be substantially unionised over the pH range 4.5 to 6.5. In this case the initial pH of the compositions of the invention will be between 7.5 and 10.

The concentration of active agent in the 10 compositions of the invention will be selected such that the change in solubility following the pH change after application of the composition to a body surface will be sufficient to produce a supersaturated solution capable of delivering an effective dose of the active agent to 15 the said body surface.

Active agent concentrations of anything from 0.00001 to 20% may therefore be suitable, depending upon the potency of the active agent and its relative solubilities 20 at the initial pH of the composition and at the pH of the body surface.

The compositions of the invention are suitable for delivering active agents for use locally (ie at the site 25 to which they are applied) or systematically through the blood stream (ie transdermal delivery). Different active agents will be suitable for different delivery means.

For local applications the following classes of active agents are preferred in the compositions of the invention: antimicrobial agents (eg antibacterial, 5 antifungal or antiviral agents), steroids, antipsoriasis agents, antiacne agents, local anaesthetics, non steroid anti inflammatory agents, antidandruff agents, headlice treating agents and antihistamines.

10 Preferred antimicrobial agents include triclosan (preferably 0.01 to 2.5%w/w), hexylresorcinol (preferably 0.05 to 5%w/w), tetracycline (preferably 0.1 to 5%w/w), miconazole (preferably 0.1 to 4%w/w), acyclovir (preferably 0.1 to 5%w/w), metronidazole (preferably 0.01 15 to 8%w/w), 4-chloro-3-methylphenol (preferably 0.1 to 10%w/w), 4 chloro-3,5-dimethylphenol (preferably 0.1 to 10%w/w) and 2,4-dichloro-3,5-dimethylphenol (preferably 0.1 to 10%w/w).

20 A preferred steroid is hydrocortisone (preferably 0.1 to 5%w/w).

A preferred antipsoriasis agent is methotrexate (preferably 0.001 to 0.5%w/w).

25

A preferred antiacne agent is retinoic acid (preferably 0.0001 to 5%w/w).

A preferred local anaesthetic is benzocaine (preferably 0.1 to 5%w/w).

5 Preferred non steroidal anti-inflammatory agents are ketoprofen (preferably 0.5 to 5%w/w), piroxicam (preferably 0.01 to 2%w/w) and diclofenac (preferably 0.1 to 5%w/w).

10 A preferred antidandruff agent is zinc omadine (preferably 0.01 to 10%w/w).

A preferred headlice treating agent is an acaricide (preferably 0.05 to 5%w/w).

15 Preferred antihistamines include mepyramine (preferably 0.1 to 5%w/w) and terfenadine (preferably 0.1 to 4%w/w).

20 For systemic applications the following classes of active agents are preferred in the compositions of the invention: anti travel sickness agents, bronchospasm relaxants, antihistamines, decongestants, antitussives, analgesics, anticoagulants, beta adrenoceptor blockers, 25 anti angina agents, anti emetics, antimicrobial agents, bronchodilators, anti allergy agents, anti migraine agents, corticosteroids and thyroid agents.

Preferred analgesics include indomethacin
(preferably 0.01 to 1% w/w) and naproxen (preferably 0.1
to 2% w/w)

5

Preferred anticoagulants include warfarin
(preferably 0.001 to 0.1% w/w).

Preferred anti-emetics include metoclopramide
10. (preferably 0.005 to 1.0 w/w).

Preferred antimicrobial agents include triclosan
(preferably 0.001 to 1.0 w/w).

15 Preferred bronchodilators include salbutamol
(preferably 0.001 - 0.5% w/w), beclomethasone (preferably
0.001 to 0.05% w/w), ipratropium (preferably 0.0001 to
0.01% w/w).

20 Preferred antiallergy agents include ketotifen
(preferably 0.001 - 0.1% w/w).

Preferred antimigraine agents include clonidine
(preferably 0.01 to 1.0% w/w) and ergotamine (preferably
25 0.0005 to 0.5% w/w).

Preferred corticosteroids include dexamethasone (preferably 0.0005 - 0.5% w/w) and prednisolone (preferably 0.001 - 0.5% w/w).

5 Preferred thyroid agent (include thyroxine (preferably 0.000005 - 0.00005% w/w).

The compositions of the invention may suitably be applied to any part of the body having sufficient 10 buffering capacity to effect a suitable pH change. This include all regions of the skin and the mucous membranes (eg the vagina, nasal passage or mouth).

It has long been known that skin has an acid pH, 15 often referred to as the "acid mantle" (the accepted pH being around 5.5 but varying from 4.5 to 6.5) which has been measured and documented extensively (Noble W.C. 1981, Microbiology of Human Skin, Lloyd-Luke Ltd). Whilst much work has been conducted to establish the pH 20 of the acid mantle, many workers agree that it is well established that the skin has a significant buffering capacity, maintained by fatty acids, proteins and the lactic acid/lactate system present in the skin. In addition, this skin acidity is maintained in spite of the 25 neutral or slightly alkaline pH of the dermis.

Preferably compositions according to the invention may further include one or more of the following agents selected from

5 i) a thickener (preferably a carbomer, e.g. Carbopol 940) - preferably in an amount of 0.1 to 5.0% w/w,

10 ii) a humectant, preferably selected from glycerol, sorbitol, propylene glycol and tricetin, (more preferably glycerol), - preferably in an amount of 0.1 to 20% w/w; and

15 iii) a solubiliser to enhance the solubility of the active agent before application to the surface of a body (preferably propylene glycol) - preferably in an amount of 0.1 to 50% w/w).

20 Optionally, the composition may contain a penetration enhancer, preferably Azone, or terpenes at a preferred amount of 0.1 to 10% w/w.

Preferably compositions according to the invention contain 30 - 99.5% water.

25

Preferably the compositions of the invention are free from agents which might act to counter the pH change

upon application to the skin (ie buffering agents) other than any inherent buffering capacity bestowed by the active agent.

5 If necessary the compositions of the invention may comprise pH adjusting agents in order that the pH before application to the skin is in the range of 3 to 4 or 7 to 12.

10 The compositions of the invention may be in any conventional form suitable for topical application, ie liquids, gels, suspensions, ointments or collodions. They may also be applied to the surface of a body predispersed on a carrier, for example as a medicated 15 plaster or a transdermal patch.

The compositions of the invention may be manufactured by any suitable conventional means. For example the active agent may be dissolved in the vehicle 20 (optionally with the aid of one or more solubilisers); any other optional soluble components may be added; the pH adjusted if necessary and any non soluble or thickening agents added.

The invention will be illustrated by the following examples:

5 Example 1

Effect of pH on ketoprofen solubility.

Run 1

10 A range of solutions comprising mixtures of 0.1M citric acid and 0.2M Na₂HPO₄ were produced having the pHs shown in table 1. A weight of ketoprofen, as shown in table 1, was added to a 20ml sample of each solution and the mixture was stirred for 24 hours at 25°C. The pH of 15 the final solution was measured.

Table 1

Original pH	amount of ketoprofen added (g)	pH on sampling after 24 hours
3	0.1	3
4	0.1	4
5	0.1	4.9
5.5	0.5	5.4
6	0.5	5.8
6.5	0.5	6
7	0.5	6.2

7.5

0.5

6.3

The concentration of ketoprofen dissolved at each pH was measured by UV spectrophotometry (at 258nm) following 5 filtration through a 0.2 um syringe filter to remove undissolved material.

The results are shown in Figure 1.

10 Run 2

Run 1 was repeated with the exception of the solutions at pH 3 and 4, as shown in Table 2.

Table 2

15

Original pH	amount of ketoprofen added (g)	pH on sampling after 24 hours
5	0.1	4.9
5.5	0.5	5.4
6	0.5	5.8
6.5	0.5	6.1
7	0.5	6.3
7.5	0.5	6.4

The results are shown in figure 1.

Run 3

Saturated solutions of ketoprofen were prepared by a different method to runs 1 and 2 to act as a check on 5 methodology.

4g of ketoprofen was added to 100 ml of deionised water and stirred at 25°C for 24 hours. The pH was tested and found to be 3.5, a sample was taken.

10

The mixture was then adjusted to a pH of 5.8 with 1M NaOH and stirred for a further 24 hours at 25°C, after which a sample was removed.

15

The mixture was adjusted to a pH of 6.4 using 1M NaOH and again stirred for 24 hours at a temperature of 25°C. A final sample was removed.

20

The three samples were filtered to remove undissolved ketoprofen (0.2 um filter) and the concentration of dissolved ketoprofen measured by the same method as in Runs 1 and 2.

25

The results are shown in figure 1.

Figure 1 demonstrates the vast change in ketoprofen solubility caused by pH changes. Similar results may be

produced for a range of ionisable active agents, and may be calculated from a solubility equation, with a knowledge of the active agents' pH and solubility in the unionised form (Physicochemical Principles of Pharmacy 5 2nd Edition, Florence and Attwood, 1988).

Example 2

Demonstration of Theoretical Supersaturation

10 Achievable from Alteration of Solution pH.

Figure 2 demonstrates the potential degrees of supersaturation achievable, with ketoprofen as the example active agent, as the pH is reduced from pH 6.4 15 (example starting point pH).

The potential degree of supersaturation achievable at each pH is determined by dividing the saturated solubility of ketoprofen at pH 6.4 with the saturated 20 solubility at each pH value of interest, where the solubility is lower than that observed at pH 6.4.

In the example shown in Figure 2, the maximum theoretical degree of supersaturation achievable with 25 ketoprofen is 513X. The maximum theoretical degree of supersaturation achievable at skin pH (for example - 5.5) is 18X. It is to be understood that further increases in

theoretical degrees of supersaturation could be achieved by increasing the starting point pH until still higher ketoprofen solubility is achieved.

5 The ketoprofen solubility values for the pH 4.9, 5.4, 5.8 and 6.3 shown on figure 2 are averages of the equivalent concentrations from runs 1 and 2. All other values are the same as in Example 1.

10 Example 3

 Stabilisation of a supersaturated solution.

An aqueous solution of 0.8% w/v ketoprofen at a pH of 10.4 was prepared at 25°C. 1% polyvinyl pyrrolidone (PVP) was added to the solution. Aliquots of 0.1M hydrochloric acid were added to the solution with stirring until a pH of 5.5 was achieved. A 4X supersaturated solution of ketoprofen was thus produced.

20 The amount of ketoprofen dissolved in the solution was measured at various times by the method used in Example 1 (after filtration through a 0.2um filter to remove undissolved ketoprofen).

25 The results are shown in Figure 3, which shows that supersaturation was maintained for at least 16 hours.

Example 4

A range of solutions having the compositions and pHs as shown in Table 3 were prepared. The amounts of 5 triclosan as shown in table 3 were added to 20 ml of each solution and the mixtures were stirred for 48 hours at 37°C. the final pH of each solution was measured.

Table 3

Original pH	Buffer composition	Amount of triclosan added (g)	pH on sampling after 48 hours
4	0.1M citric acid	0.1	4.1
	0.2M Na ₂ HPO ₄		
5	0.1M citric acid	0.1	5.2
	0.2M Na ₂ HPO ₄		
6	0.1M citric acid	0.5	6.3
	0.2M Na ₂ HPO ₄		
7	0.2M NaH ₂ PO ₄	0.5	7.1
	0.2M NaH ₂ PO ₄	.	
8	0.2M Na ₂ HPO ₄	0.5	8.1
	0.2M NaH ₂ PO ₄		
9.2	0.1M Na ₂ CO ₃	1	9.6
	0.1M NaHCO ₃		
10.1	0.1M Na ₂ CO ₃	1	10.6
	0.1M NaHCO ₃		

Samples of each mixture were centrifuged at 3000 rpm for 10 minutes to remove undissolved material. The concentration of dissolved triclosan was measured in each solution by HPLC using a standard procedure (detection at 5 281nm).

The solubility of triclosan at each pH is shown in Figure 4.

10 The supersaturation potential of a solution at pH 10 containing 200ppm triclosan was calculated by dividing the concentration of triclosan in that solution by the concentration of triclosan in the solutions at lower pHs.

15 These theoretical values are also shown in Figure 4. Thus it can be seen that the degree of supersaturation achievable at a skin pH (eg 5.5) is 30X if a 200ppm triclosan solution at pH 10 is used as the starting composition. It is to be understood that higher degrees 20 of supersaturation may be achieved by increasing the triclosan concentration in solution at pH 10, or further by increasing the pH of the starting composition.

Example 5

Topical gel

	% w/w
Acyclovir sodium salt	2.0
Carbopol 940	1.0
Polyvinyl pyrrolidone	1.0
Propylene glycol	10.0
Deionised water	86.0
	100.00

5 The pH of the formulation is adjusted to ensure a pH of
10.0.

Upon application to the skin the change in pH of the
composition to between 4.5 and 6.5 will result in the
formation of an approximately 10X supersaturated
10 composition.

Example 6

Topical gel

	% w/w
Piroxicam	0.2
Carbopol 940	1.0
Hydroxypropylmethyl cellulose	2.0
Triethanolamine	0.2
Propylene glycol	50.0
Deionised water	46.6
	100.00

The pH of the formulation is adjusted to ensure a pH of 9. Upon application to the skin, the change in pH of the composition to between 4.5 and 6.5 will result in the formation of an approximately 10X supersaturated
5 composition.

Claims

1. A pharmaceutical composition for topical application comprising

5 a) a pharmaceutically active agent, and
 b) a pharmaceutically acceptable vehicle,
 the composition having a pH of 7 to 12 or a pH of 3 to
 4,

characterised in that the pharmaceutically active agent
10 is dissolved at or below its saturation concentration and
 that the composition becomes supersaturated when the pH
 is changed to between 4.5 to 6.5.

2. A composition as claimed in Claim 1 which further
15 comprises an anti-nucleating agent.

3. A composition as claimed in Claim 1 or Claim 2 wherein
 the pharmaceutically active agent is an acid having a pKa
 of 6.5 to 10, a base having a pKa of 4 to 4.5, or an
20 amphoteric agent having an acid pKa of 6.5 to 10 and a
 base pKa of 4 to 4.5.

4. A composition as claimed in any preceding claim
 wherein the pharmaceutically acceptable vehicle is water
25 or a mixture of water and alcohols.

5. A composition as claimed in any preceding Claim further comprising at least one of

- a) 0.1 to 5.0% w/w, of a thickener,
- b) 0.1 to 20% w/w of a humectant,
- c) 0.1 to 50% w/w of a solubiliser, or
- d) 0.1 to 10% w/w of a penetration enhancer.

6. A pharmaceutical composition for topical application as hereinbefore described with reference to Examples 5
10 and 6.

27

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9522885.4

Relevant Technical Fields		Search Examiner MRS S E CHALMERS
(i) UK Cl (Ed.O)	A5B: BLB, BLC, BLD, BNB	Date of completion of Search 5 FEBRUARY 1996
(ii) Int Cl (Ed.6) A61K: 9/06, 9/08, 9/10, 9/107		Documents considered relevant following a search in respect of Claims :- 1-6
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: WPI; CLAIMS		

Categories of documents

X:	Document indicating lack of novelty or of inventive step.	P:	Document published on or after the declared priority date but before the filing date of the present application.
Y:	Document indicating lack of inventive step if combined with one or more other documents of the same category.	E:	Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A:	Document indicating technological background and/or state of the art.	&:	Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
A	EP 0272045 A2	(BEECHAM)	
A	EP 0271332 A2	(BEECHAM)	
A	WO 93/20799 A1	(SMITH-KLINE BEECHAM)	

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).